REMARKS

Upon entry of the instant amendment, claims 1, 2, 4, 6 and 17 will be amended, claim 16 will be canceled, and claim 27 will be added, whereby claims 1, 2, 4-15 and 17-27 will remain pending. Claim 1 is the sole independent claim.

Claim 1 is amended herein to even more clearly define Applicant's invention by reciting that it is directed to a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least two ligands, the ligands having an affinity for both a free target and a non-free target so that the free target can be recognized by the ligands at an equivalent level as the non-free target when not bound to the microparticle, said at least two ligands having a dissociation constant with the free target and non-free target of at least about E-8 (M), said at least two ligands are bound to a surface of the microparticle forming a ligand-bonded complex having increased affinity to the non-free target, the increased affinity of the ligand-bonded complex allowing specific binding of the ligand-bonded complex to a non-free target in the presence of both a non-free target and a free target.

The amendment to claim 1 is in accordance with the originally filed disclosure and does not constitute new matter. For example, the Examiner's attention is directed to page 2, the first full paragraph wherein it is disclosed that surprisingly it has been found that a ligand-bonded complex, to which plural numbers of a ligand having a low affinity to a target substance were bonded, had a high reactivity to a non-free target such as a cancer cell even in the presence of a free target substance. Still further, the Examiner's attention is directed to page 3, the first full paragraph, page

5, the third and fourth full paragraphs and the Examples including page 14, the second full paragraph, and originally filed claim 2.

Claim 27 has been added to further define Applicants' invention with the disclosure such as at page 2, line 18.

Still further, the claims have been amended herein to make amendments of a cosmetic nature, and no estoppel should be associated with these amendments.

Moreover, the specification has been amended to explicitly include the language in amended claim 1.

Reconsideration and allowance of the application are respectfully requested.

Rejection Under 35 U.S.C. 112, Second Paragraph

In response to the rejection of claims 1, 2 and 4-26 under 35 U.S.C. 112, second paragraph, Applicants respectfully submit the following.

The claims have been amended herein to advance prosecution by removing terminology that is criticized as being indefinite. However, Applicants note that one having ordinary skill in the art would readily understand the claim terminology either prior to or subsequent to the present amendment. For example, one having ordinary skill in the art would readily understand that the claims also include substantially an equivalent level in reciting that the ligands have an affinity for both a free target and a non-free target so that the free target can be recognized by the ligands at an equivalent level as the non-free target when not bound to the microparticle.

Moreover, Applicants note that claim 1 has been clarified to recite that at least two ligands are bound to the surface of the microparticle.

In view of the above, the indefiniteness rejection under 35 U.S.C. 112, second paragraph, should be withdrawn.

Rejections Based Upon Prior Art

The following rejections are set forth in the Office Action:

(a) Claims 1, 2, 5, 7-14, 16, 17, 19-22 and 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Tagawa et al. (hereinafter "Tagawa"), U.S. Patent No. 5,264,221.

(b) Claims 1, 2, 4, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. (hereinafter "Li"), U.S. Patent No. 5,512,294.

(c) Claims 6, 15 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagawa in view of Allen et al. (hereinafter "Allen"), U.S. Patent No. 5,527,528.

(d) Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tagawa in view of Lindhofer et al. (hereinafter "Lindhofer"), U.S. Patent No. 6,294,167.

With respect to the rejections based on anticipation, the rejections are asserting that each of Tagawa and Li disclose plural numbers of the ligand. Moreover, the rejections are asserting that one of skill in the art would recognize that the liposomes of Tagawa and Li would comprise more than one of the antibodies on its surface.

Moreover, the rejections assert that the ligand of Tagawa or Li would possess the property of having affinity for both a free target and a non-free target so that the free target can generally be

recognized by the ligand at substantially equivalent level as the non-free target when not bound to the microparticle. In particular, the rejections are asserting that the prior art would inherently have the characteristics as recited in Applicants' claims.

With the respect to the obviousness rejections, the rejections are asserting, that, with respect to claims 6, 15 and 23, it would have been obvious to couple antibodies to polyethylene glycol molecules as taught by Allen into the liposome of Tagawa because Allen shows that the coupling of antibodies to the PEG molecule allows the antibody in the polymer layer to be positioned at a selected depth in the layer as shown to increase or decrease the extent to which the antibody is buried in the polymer layer.

With respect to claim 18, the obviousness rejection asserts that it would have been obvious to incorporate pharmaceutical compositions as taught by Lindhofer with the liposomes of Tagawa because Lindhofer shows that these compositions provide for particular tumor cells to be distinguished from other cells on account of the recognition of specific marker antigens and are therefore suitable for immunological cell therapy and the pharmaceutical compositions lend themselves to *in vivo* and *in vitro* therapy of different tumor parts.

In response to the rejections of record, Applicants respectfully submit the following.

Applicants point out that their invention, as recited in independent claim 1, is directed to a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least two ligands, the ligands having an affinity for both a free target and a non-free target so that the free target can be recognized by the ligands at an equivalent level as the non-free target when not bound to the microparticle, said at least two ligands having a dissociation constant with the free target and

non-free target of at least about E-8 (M), said at least two ligands are bound to a surface of the microparticle forming a ligand-bonded complex having increased affinity to the non-free target, the increased affinity of the ligand-bonded complex allowing specific binding of the ligand-bonded complex to a non-free target in the presence of both a non-free target and a free target.

As discussed in Applicants' originally filed application, a characteristic feature of the present invention is the use of at least two ligand molecules, which can be those of a single kind of ligand, such as an antibody, attached on the surface of the microparticle. For example, two or more independent ligand molecules may be attached on the surface of the microparticle, or alternatively, two or more ligand molecules may be crosslinked and the crosslinked polymolecule may be attached on the surface of the microparticle. For example, the Examiner's attention is directed to Applicants' specification, in the paragraph beginning at page 5, third line from the bottom of the page, and demonstrated by 1-3-1 antibody polymer (poly 1-3-1) in Example I.

The use of plural numbers of the at least one ligand, i.e., two or more of the ligand molecules, provides the advantages associated with Applicants' invention because the ligand molecule itself only has low affinity to the target, as explained, for example, at page 3, lines 8 to 9, of Applicants' specification where, for example, a dissociation constant between the target substance and one ligand is E-8 M or more. If the microparticle is bound with only one ligand, the resulting microparticle cannot react with both of free target and non-free target. Whilst, the microparticle according to the present invention, bound with two or more ligands having low affinity to the target, can react selectively with the non-free target when the free target coexists.

It is generally believed that, by carrying out an ordinary reaction to introduce a ligand molecule, such as an antibody onto the surface of a microparticle, which is commonly available in the art, several numbers, for example, about 10 to 20, of the ligand molecules are introduced to the surface of the microparticle. It is also believed that introduction of only one ligand molecule to the microparticle is hardly attainable. Accordingly, in general, the rejections are correct in asserting that microparticles modified with an antibody are believed to have plural numbers of ligands on the surface of the microparticle. This is also the case with the presently claimed invention. However, according to the presently claimed invention and in contrast to the prior art utilized in the rejections, the two or more ligands that are used have low affinity to the target. Therefore, the prior art of record does not teach or suggest Applicants' disclosed and claimed invention wherein the plural ligands have low affinity to the target.

The Examiner is reminded that Applicants' specification in the Background Art section, discloses that targeting therapies using antibody-bonded complexes are based on high specificity of the ligand to a target, and therefore, superior therapeutic effect and reduced side effect can be expected. It is disclosed that in the targeting therapy, a problem has been pointed out in that an antibody-bonded complex reacts with a free target such as a free antigen existing in blood or the like, and thus a sufficient amount of the drug cannot react with a solid tumor tissue, including a primary lesion and a metastatic foci, having non-free antigens and the like. In other words, it is disclosed that when a part of antigens are secreted into blood or antigens are released from cancer cells free antigens (soluble antigens) appear in blood, as observed in certain types of cancers, antibody-bonded complexes will react with the free antigens to form immuno-complexes, thereby

the reaction with target cells will be inhibited. Accordingly, it is disclosed in order to design an antibody-bonded complex, it is generally required to chose an antibody whose antigen is absent or at an extremely low level in blood. Further, it is disclosed than an antibody against an antigen, whose significance in serum diagnosis has been established clinically, is impossible to use in the manufacture of an antibody-bonded complex.

As disclosed in the "Disclosure of the Invention" section of Applicants' specification, in order to solve the aforementioned problems, the inventors of the present invention conducted researched on the relationship between soluble target substances, such as a free antigen and ligands, such as an antibody. Surprisingly, it was found that a ligand-bonded complex, to which plural numbers of a ligand having low affinity to a target substance were bonded, had a high reactivity to a non-free target, such as a cancer cell, even in the presence of a free target substance.

From the above, it is apparent that, in the prior art, a particular kind of antibody is selected so as to be able to bind to non-free target, but not bind to free-target. In contrast, according to the present invention, an antibody having low affinity both for non-free target and free target is used, and by using plural numbers of the antibody, a selective affinity for the non-free target is achieved.

Regarding the prior art utilized in the rejections of record, neither Tagawa nor Li teaches or suggests Applicants' invention which includes, amongst other features, that the at least two ligands have a dissociation constant with the free target and non-free target of at least about E-8 (M), the at least two ligands are bound to a surface of the microparticle forming a ligand-bonded complex having increased affinity to the non-free target, and the increased affinity of the ligand-bonded complex allowing specific binding of the ligand-bonded complex to a non-free

target in the presence of both a non-free target and a free target.

The rejection based upon Tagawa makes assertions regarding the use of similar human cell-reactive monoclonal antibody as disclosed for the present invention. However, as noted above the ability of ligands to provide the advantageous ligand-bonded complex according to the present invention depends upon the binding affinity of the ligand. Also, as noted above, the ligands according to the present invention have a low binding affinity. For example, the Examiner's attention is once again directed to Applicants' Examples. In this regard, attention is specifically directed to page 14, wherein the results are discussed and it is indicated that the results demonstrate that the poly 1-3-1 antibodies had a much higher reactivity to the immobilized α-enolase compared with the 1-3-1 antibody, and both of the 1-3-1 antibody and the poly 1-3-1 antibody had substantially no reactivity to the free antigen. Therefore, the Example notes that it is suggested that, when a ligand-bonded complex is produced, the reactivity to an immobilized antigen can be enhanced and the reactivity to a free antigen can be reduced by binding plural antibody molecules, having such affinity as that of the 1-3-1 antibody, as ligands to a microparticle.

Moreover, Applicants note that the VCAM-1 antibody, as a non-polymerized antibody, which is disclosed in the Comparative Example has a high affinity to the target, dissociation constant of E-9 M, and is therefore distinct from the ligands according to the present invention.

Regarding the assertion that it would have been obvious to one of ordinary skill in the art to incorporate polyalkylene glycol as taught by Tagawa with the liposome of Allen because Tagawa shows that the use of polyalkylene glycol provides a drug-containing antibody-bonded liposome having the nature of being captured in the reticuloendothelial system improved. However, whether

or not it would have been obvious to modify Allen in the manner asserted in this rejection, Applicants' invention would not be at hand.

Moreover, the rejections further assert that Tagawa does not teach a ligand-bounded complex in a pharmaceutical composition, but that Lindhofer discloses such and motivates its use in Tagawa. In response, Applicants respectfully submit that there is no motivation to combine the disclosures of Tagawa and Lindhofer. However, for the sake of brevity, arguments in this regard are not being expanded upon herein, because of the deficiencies associated with any combination of the disclosures of these documents. In particular, the above noted deficiencies of Allen are not in any manner overcome by any disclosure of Lindhofer. Accordingly, this ground of rejection should also be withdrawn.

Thus, Applicants respectfully submit that Applicants' claims patentably define their invention, whereby withdrawal of the rejections of record is respectfully requested.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the objections and rejections of record, and allow all the pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions or wish to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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